## REMARKS

New claims 94-96 have been added. Support for the new claims is found on page 11, line 35, to page 12, line 3, of the specification. Claims 1, 11, 36, 42, 43, 82-88, 90-96 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

### I. The Rejection of Claims 1, 11, 36, 42-43, 82-88, and 90-93 under 35 U.S.C. § 103

Claims 1, 11, 36, 42-43, 82-88, and 90-93 remain rejected under 35 U.S.C. § 103 as being unpatentable over Wilson *et al.* (*PNAS* 96: 12833-12838, 1999) in view of Cao *et al.* (*Mol. Microbiol.* 45: 1267-1276, 2002) for the reasons of record. This rejection is respectfully traversed for the reasons of record and further for the reasons stated below.

The Office asserts that it would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain used in DNA hybridization microarrays of Cao *et al.* to the Wilson *et al.* method for determining the mode of action of an antimicrobial compound comprising detecting hybridization complexes and assigning a mode of action in order to obtain an antimicrobial mode of action for *B. subtilis* which is known to be resistant to known antimicrobial drugs. Applicants respectfully point out that the Office has ignored the record in this case and remade assertions that have been withdrawn or are not supported therein.

First, the Office states "that the specification does not define subinhibitory amount to be above or below the minimum inhibitory concentration of INH". As pointed out by Applicants in the Amendment of May 2, 2007, the term "sub-inhibitory amount" is defined on page 11, line 35, to page 12, line 3, of the specification, which states: "The bacterial cells are cultured in the absence and presence of at least one sub-inhibitory amount of an antimicrobial compound of interest. The sub-inhibitory amount is based on the MIC of the antimicrobial compound against a bacterium and cultivation of the bacterium at one or more concentrations below the MIC. Preferably, the sub-inhibitory amount is 0.5X MIC, more preferably 0.25X MIC, and most preferably 0.1X MIC." The term minimal inhibitory concentration (MIC) is defined on page 11, lines 1-5, of the specification, which state: "Minimal inhibitory concentration (MIC) may be known, or the compound and/or the MIC for the compound may be unknown. The determination of the MIC is well within the capability of those skilled in the art. MIC is defined as that concentration of an antimicrobial compound resulting in no visible growth of the organism." The specification on page 11, line 35, to page 12, line 3, of the specification clearly states that

"sub-inhibitory amount" is below the MIC. Moreover, the Office rejected the term "sub-inhibitory amount " in the Office Action of November 2, 2006 and the Advisory Action of June 1, 2007, but in response to Applicants' argument of July 18, 2007 withdrew its rejection under 35 U.S.C. § 112, second paragraph in the Office Action of September 25, 2007.

Second, the Office states "it would appear that subinhibitory means an amount that is not able to kill the bacteria". Again the record and the specification are contrary to this statement by the Office, as stated above. The specification states on page 11, lines 3-5: "MIC is defined as that concentration of an antimicrobial compound resulting in no visible growth of the organism". Consequently, the MIC results in no growth. Subinhibitory concentrations would result in growth.

Third, the Office states: "The 0.2 µg/ml or 1 µg/ml for INH taught by Wilson *et al.* clearly does not kill the bacteria, and meets the limitation of a subinhibitory amount". This is incorrect since Wilson *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml, which are above the minimum inhibitory concentration of INH, *i.e.*, 0.02 µg of INH per ml.

Fourth, the Office states: "Schaaf et al. (Eur J. Clin. Microbiol. Infect. Dis. 2006. Vol. 26:203205) teach the minimal inhibitory concentration (MIC) of isoniazid (INH) of low level INH-resistant organisms is 0.2 -5 µg/ml. Therefore the 0.2 µg/ml is far lower than the MIC amount of 5 µg/ml. Therefore in the alternative, even if the "subinhibitory amount" were defined by the MIC number, Wilson et al. teach a subinhibitory amount and applicants arguments and statements are not found persuasive". Preliminarily, Applicants point out that Schaaf *et al.* published on February 9, 2007, which is after the priority date of the instant application. Also Schaaf *et al.* state on the first page of the article that "[t]he critical concentration for high-level INH resistance is defined as >1.0 g/ml", not 0.2 µg/ml as the Office states above. Moreover, the cited reference is inappropriate because Schaaf *et al.* disclose isoniazid-resistant mutants, which is not what Wilson used. Moreover, even if Wilson did use one of these mutants, 0.2 µg/ml is not below the resistant MIC range of 0.1-5 µg/ml described for *Mycobacterium*. Consequently, Applicants submit that the Office's statement is simply incorrect.

Fifth, the Office states: "Wilson et al., clearly and specifically teach the growth and drug treatment of the strain wherein cultures grown and treated with 0.2 µg/ml or 1 µg/ml the antimicrobial compound which meet the limitations of subinhibitory amounts contrary to Applicants assertions." The Office's assertion is simply incorrect and not supported by the record. Wilson *et al.* teach the use of DNA microarrays to characterize the global transcriptional

response of *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml. The minimum inhibitory concentration of INH is 0.02 µg of INH per ml. The concentrations of 0.2 µg or 1 µg of INH per ml used by Wilson *et al.* are above the MIC.

Applicants submit that Wilson *et al.* and/or Cao *et al.* do not teach or suggest the instant invention. Wilson *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml, which are above the minimum inhibitory concentration of INH, *i.e.*, 0.02 µg of INH per ml. Cao *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Bacillus subtilis* to vancomycin at concentrations 10X the minimum inhibitory concentration. Both of the cited references use inhibitory concentrations, not sub-inhibitory concentrations as claimed in the instant application.

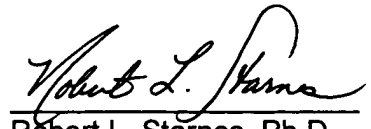
Consequently, Applicants submit that Wilson *et al.* in view of Cao *et al.* implicitly teach away from using sub-inhibitory amounts of an antimicrobial compound. One of ordinary skill in the art would not be motivated by the cited references to use sub-inhibitory amounts of an antimicrobial compound.

For the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. § 103 have been overcome and respectfully request reconsideration and withdrawal of the rejections.

## II. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



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